REMARKS

Favorable reconsideration is respectfully requested in view of the following remarks.

I. CLAIM STATUS

Claims 1-12 were pending in this application when last examined.

Claims 1-4 and 9-11 were examined on the merits and stand rejected.

Claims 5-8 and 12 were withdrawn as non-elected subject matter.

II. OBVIOUSNESS REJECTION

On pages 2-5 of the Office Action, claims 1-4 and 9-11 were newly rejected under 35 U.S.C. § 103(a) as obvious over Graham (1984), Fu et al., and Chen et al. or Snaith et al., in light of Graham et al. (reference AO in the February 22, 2002 IDS) ("Graham (1991)").

This rejection is respectfully traversed for the reasons set forth in the response filed November 16, 2006 and for the following reasons.

The cited art references fail to teach each and every element of the claimed invention, and they lack a reasonable expectation of success in combining their teachings to arrive at the claimed invention.

As noted in the last response, the specification (at page 3, last paragraph, to page 4, second paragraph) describes the method in the primary reference of Graham (1984). In particular, this reference discloses a method for constructing a recombinant adenovirus vector using a circular DNA constructed by inserting a small plasmid at the restriction enzyme Xba I site, which site exists at the one location in the E1 region of the adenovirus 5 type, and then transfection to a mammalian cell line (the 293 cells). It was reported that the circular DNA produces the infectious virus. See also the Abstract on page 2917 of Graham (1984). Graham (1984) suggests that a recombinant adenovirus vector can be constructed by replacing the E1 region or E3 region of a circular adenovirus DNA with an exogenous gene.

However, the method in Graham (1984) differs from that of the instant invention in that when a recombinant adenovirus vector is actually constructed using the method in Graham (1984), two problems arise. First is the problem of low efficiency in incorporating the expression cassette into the extremely large plasmid which contains the adenovirus genome DNA. Second, the plasmid DNA portions remain in the constructed adenovirus vector. See page 4, lines 6-12 of the disclosure.

The Applicants were the first to recognize and solve these problems with the present invention. The method of the present invention does not have a low efficiency of incorporating the expression cassette and it deletes the cosmid vector. The deletion of the cosmid sequence means that the resultant recombinant adenovirus vector does not retain the plasmid DNA portions as in Graham (1984). Thus, the method of the present invention results in a ***structurally different*** recombinant adenovirus vector from that in Graham (1984). Therefore, Graham (1984) does not teach the present invention as essentially claimed.

Fu et al. only solved the first problem noted above with regard to the method in Graham (1984). Fu et al. did not solve the second problem with respect to the method in Graham (1984). In this regard, the vector Ad COS in Fu et al. comprises "adenovirus DNA" and "cosmid sequence". Thus, Fu et al. did not recognize or solve the second above-noted problem with regard to the method in Graham (1984), *i.e.*, the problem of plasmid DNA portions remaining in the constructed adenovirus vector.

Thus, the combination of Graham (1984) and Fu et al. fails to arrive at the claimed invention, as the methods described therein result in ***structurally different*** recombinant adenovirus vector from that of the present invention.

Further, it is well established that there can be no motivation where the cited references teach away from the combination. The prior art must be considered in its entirety and that references cannot be combined where the references teach away from their combination. See M.P.E.P. § 2145 X, D, 2. A reference can be said to teach away when a person of ordinary skill in the art, upon reading the reference, would be ***discouraged*** from following the path set out in the reference, or would be ***led in a direction divergent from the path taken by the applicant*** or if

it suggests that the line of development flowing from the reference's disclosure is ***unlikely to be productive*** of the result sought by the applicant.

It is respectfully submitted that the cited prior art references ***teach away*** from the claimed invention.

For instance, Graham (1984) teaches that the size of Ad5 vector is 36 kb and it can ***only take 2kb extra DNA***. See the description of Figure 1 on page 2917 of Graham (1984), wherein Graham (1984) discloses the maximum size of DNA which can be inserted into Ad5 DNA without exceeding packaging constraints is 2kb. Accordingly, prior to the instant invention, the state of the art as represented by Graham (1984) was such that: (i) a recombinant adenovirus vector should be limited in size to within 38kb in order to maintain the ability to infect animal cells and produce infectious virus particles; and (ii) an expression cassette to be incorporated into the Ad5 vector should be within 2kb.

It is respectfully submitted that such a teaching in Graham (1984) constitutes a ***teaching-away*** from the claimed invention, which calls for ***about 4-5kb***.

Further, the size of adCOS in Fu et al is about 40kb, which ***exceeds*** the recommended 38 kb limit. Accordingly, based on such teachings in Graham (1984) and Fu et al., one of ordinary skill in the art at the time of the invention would believe the vector adCOS in Fu et al. is ***not*** infectious and cannot take any further extra DNA.

Accordingly, one of ordinary skill in the art would be ***lead in a path divergent*** from the present invention.

Further, there would be ***no reasonable expectation of success*** in combining Fu et al. with Graham (1984) as the references would lead the skilled artisan to believe that there combination would result in an inoperative or unsatisfactory for its intended purpose. Accordingly, the references lack a reasonable expectation of success of modifying their teachings to arrive at the claimed invention of a recombinant adenovirus of about 38kb containing an expression cassette of about 4-5kb, because Graham (1984) teaches only 2kb can be inserted (not 4-5kb) and a recombinant adenovirus vector should be limited in size to within 38kb (not 40kb as in Fu et al.).

Chen et al. fail to remedy the deficiencies of Graham (1984) and Fu et al.

Chen et al. also fail disclose the structural components of the claimed adenovirus vector. Nor does the reference recognize and solve the above-noted problems associated with the method in Graham (1984). The Office relied on Chen et al. for disclosing the action of different recombinases on the adenovirus genome. However, Chen et al. is silent as to the insertion site of the expression cassette and the specific structural components of the adenovirus vector of the claimed invention. Thus, in a situation where the necessity for deletion of a base vector has not been recognized, one of ordinary skill in the art would not conceive of the idea of using the recombination system of Chen et al.

For these reasons, the combination of Graham (1984), Fu et al. and Chen et al. fails to arrive at the claimed invention as the methods described therein result in ***structurally different*** recombinant adenovirus vector from that of the present invention. Also, the cited references lack a reasonable expectation of success in view of the various ***teachings away*** within the references..

The above arguments were made in the response filed November 16, 2006 in reply to the 103(a) obviousness rejection over Graham, Fu and Chen in the Office Action dated May 16, 2006. The Office found such arguments to be unpersuasive in view of the newly cited references of Snaith et al. and Graham et al. (1991).

Snaith et al. fails to remedy the above-noted deficiencies in the primary references. The Office relied on Snaith et al. as disclosing the *Flp* recombinase and the recognition sequence thereof, which is FRT. Snaith et al. mentions nothing regarding the deletion as to the insertion site of the expression cassette and the specific structural components of the adenovirus vector of the claimed invention.

As to Graham (1991), the Office appears to rely on this reference to remedy the deficiencies of the primary references. The Office contends that Graham et al. (1991) (on page 111, last paragraph) disclose that the maximum size of the virus to be packaged is 38 kb, and to incorporate larger DNA segments, it is necessary to delete appropriate amounts of viral DNA. According to the Office, Graham et al. (1991) discloses that E1 and E3 can contain deletions, 1.9kb (about 2kb) in E3 and 3kb in E1.

However, the teachings in Graham et al. (1991) appear to be prophetic and lack any reasonable expectation of success. In this regard, at page 111 of Graham et al. (1991) (i.e., the portion of the reference relied upon by the Office), Graham et al. (1991) discloses that "[c]ombining E1 and E3 deletions in a single vector should result in a capacity of approx 7 kb." However, it does not appear that Graham et al. (1991) ever actually made such a vector.

Further, the Office contends that "one of skill in the art would have known that non-essential DNA form the virus (i.e., the recombinant cosmid/adenovirus vector) must be deleted, and that the cosmid was not required for the virus. See the bottom of page 4 of the Action. However, it is respectfully submitted that none of the cited references actually disclose or suggest such. How would the skilled artisan know of the necessity for deletion of such non-essential DNA? In this regard, kindly note that Fu et al. disclose a recombinant adenovirus vector in which the cosmid DNA is contained therein, and Fu et al. asserts the effectiveness of such an adenovirus vector. Accordingly, one of ordinary skill in the art, upon reading the cited references as represented by Fu et al, would be lead to retain the cosmid sequences. Thus, in contrast to the Office's position, the cited references ***actually teach away*** from concept of the present invention.

The inventive concept of the present invention is that any DNA should be deleted from the recombinant cosmid/adenovirus vector for providing the vector with infectious ability (i.e., downsizing up to 38kd). Again, Fu et al. clearly does disclose this concept and, in fact, ***teaches away*** from such.

It is respectfully submitted that Applicants were the first to recognize and provide a novel method for producing a recombinant vector (38kb) of an adenovirus genome DNA (33-34kb) and an expression cassette (4-5kb). The Applicants were the first to recognize that the deletion of a base vector is essential for constructing an infectious recombinant adenovirus containing a large-sized expression cassette.

For these reasons, the above-noted obviousness rejection of claims 1-4 and 9-11 is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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